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Developmental Aspects of Long QT Syndrome Type 3 and Brugada Syndrome on the Basis of a Single *SCN5A* Mutation in Childhood

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OBJECTIVES The aim was to investigate at what age electrocardiographic characteristics of long QT syndrome type 3 (LQT3) and Brugada syndrome (BS), based on a single *SNC5A* mutation, appear.

BACKGROUND The QT interval (QT) in LQT3 is prolonged during bradycardia. It is not clear yet if this is obvious in young children with a relative fast heart rate (HR).

METHODS Thirty-six children with an *SNC5A* gene mutation (1795insD) and 46 non-carrier siblings were investigated. In different age groups, HR, QT, QT_c, and ST-segment elevation on a 12-lead electrocardiogram (ECG), and HR, QT, QT_c, and ΔQT after the longest pause in a Holter (recording) were evaluated.

RESULTS In all age groups, HR at rest tended to be lower in carriers than in non-carriers, and QT was longer in carriers than in non-carriers. The Brugada phenotype was found >5 years. Gender specific differences were not identified. The QT at lower HR and ΔQT were longer in carriers than in non-carriers. A QT_c of ≥0.44 s at the lowest HR (sensitivity 100%; specificity 88.4%) and ΔQT ≥60 ms (sensitivity 100%; specificity 82.6%) were good predictors for having LQT3.

CONCLUSIONS We conclude that electrocardiographic characteristics of LQT3 and BS show age-dependent penetrance. A QT prolongation and conduction disease were present from birth onwards, whereas ST-segment elevation only developed >5 years. Good tools for clinical diagnosis of LQT3 in this family are QT_c at the lowest HR and ΔQT after a pause in a Holter, even at very young age. (J Am Coll Cardiol 2005;46:331–7) © 2005 by the American College of Cardiology Foundation

The QT interval (QT) in congenital long QT syndrome type 3 (LQT3) is disproportionally prolonged during bradycardia (1). Mutations in the cardiac sodium channel gene *SCN5A* are responsible for LQT3 (2), Brugada syndrome (BS) (3), and isolated cardiac conduction disease (4–6). We recently described a large eight-generation family with >200 adults characterized by premature nocturnal sudden death, LQT3, and BS (7). The underlying genetic defect was a mutation in *SCN5A* (TGA insertion at position 5537 leading to the insertion of aspartic acid (1795insD) within the C-terminal domain) (6,7).

In LQT3, symptoms generally occur after puberty (8,9), and in BS, the electrophysiological phenotype is most prevalent in the third decade. In both syndromes, male subjects seem to be at increased risk (10,11). In our family, we followed children, some shortly after birth, to investigate several clinical parameters in relation to age, gender, and genotype. The aim of the study was to establish the age of onset of the electrocardiogram (ECG) patterns of LQT3 and BS.

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METHODS

Patients. We included all but four (refusal of genetic evaluation) children (age <16 years) from this family, who were genetically proven to be carrier or non-carrier of the 1795insD *SCN5A* mutation. All parents and children ≥12 years provided written informed consent for clinical and genetic evaluation. Data were collected between 1965 and 2002 and in different age groups (0 to 1, 1 to 3, 3 to 5, 5 to 8, 8 to 12, and 12 to 16 years). Since the genetic analysis (year 2000), the children could be divided into carriers and non-carriers.

Monitoring parameters. The children were evaluated by history, ECG (12-lead), Holter recording (Holter), ergometry, and signal-averaged electrocardiogram (SAECG).

In the ECG (supine position), heart rate (HR [beats/min]), PQ interval (PQ [ms]), QRS width (ms), occurrence of right bundle branch block (RBBB) (rSR′ ≥90 at <4 years; ≥100 at >4 years), J waves (rounded second wave of QRS interval), ST-segment elevation (≥1 mm in V_1, V_2, or V_E [under xiphoid bone]; measured 40 ms after the J-point), QT, and QT_c (ms; lead II; Bazett [12]) were evaluated.

In the Holter, mean, lowest, and highest HR, QT at different HR, QT_c at the lowest HR, ΔQT (QT after the longest pause minus the QT of the preceding QRS interval;

Abbreviations and Acronyms

AP = action potential
BS = Brugada syndrome
ECG = electrocardiogram
HR = heart rate
I_{to} = transient outward current
LQT3 = long QT syndrome type 3
SAECG = signal-averaged electrocardiogram

a pause was defined as an R-R that was >50% longer than the preceding R-R; Fig. 1), longest R-R, AV conduction, and rhythm disturbances were analyzed. All parameters in ECG and Holter before pacemaker implantation were evaluated at least every three years.

During ergometry (>8 years; bicycle test), HR at rest, exercise, and recovery, and QT at different HR were measured (13).

In SAECG (>5 years; 40 Hz), QRS interval width (ms), D40 (ms; time in which the voltage <40 μV at end of QRS interval), V40 (μV; root mean square voltage for terminal 40 ms of QRS interval), and late potentials (LP) were measured (14).

Statistical analysis. Data are expressed as mean ± SD. A two-tailed Student *t* test for unpaired samples (with equal or unequal variances, determined with F-ratio testing) or Fisher exact test was performed. A $p < 0.05$ was considered statistically significant. Sensitivity and specificity of QT_c and ΔQT were calculated with the 2 × 2 method for determining predictive values of a diagnostic test.

RESULTS

Patient characteristics/history. Mean age at first visit was 7.1 ± 5.0 for carriers (n = 36; 21 boys and 15 girls) and 5.9 ± 2.1 years for non-carriers (n = 46; 24 boys and 22 girls). None of the carriers had complaints; they only came to our attention because of identification of the disorder in one of the parents. Total follow-up period for carriers and non-carriers was 9.6 ± 9.3 years versus 10.8 ± 7.2 years. Follow-up period until pacemaker implantation (n = 30; 5 AAI, 14 VVI, 11 DDI) for carriers was 3.6 ± 5.9 years. During follow-up, no sudden death occurred.

ECG. In all age groups, HR at rest tended to be lower in carriers than in non-carriers, but was within the normal range for age (Table 1) (15). The PQ was not different between carriers and non-carriers (data not shown). The QRS width was mostly longer in carriers (Table 1). We found no signs of RBBB or J waves in either group. The QT was longer in carriers in every age group (Fig. 2A). Similar results were found for QT_c; QT_c in carriers increased with age (0.39 ± 0.02 s at 0 to 1 year vs. 0.49 ± 0.06 s at 12 to 16 years; $p < 0.001$). An ST-segment elevation ≥1 mm occurred more often in carriers >5 years (5 to 8 years: $p = 0.09$; 8 to 12 and 12 to 16 years: $p < 0.05$; Table 1; Figs. 2B and 3). The ST-segment elevation was ≥2 mm in 0%, 20%, 50%, and 80% of the children <5, 5 to 8, 8 to 12, and 12 to 16 years, respectively. There were no differences between male and female carriers in the aforementioned parameters, including QT_c (boys, 0.44 ± 0.06 s vs. girls 0.44 ± 0.04 s; other data not shown) and ST-segment elevation.

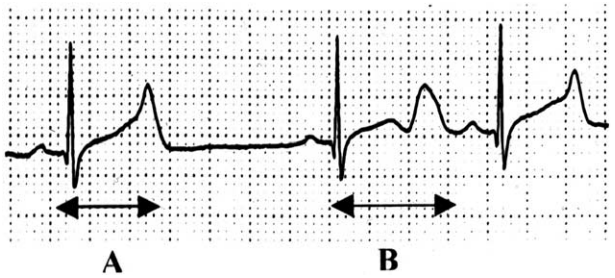

Figure 1. ΔQT = QT interval after the longest pause in a Holter recording minus QT of the preceding QRS interval (**B** − **A**).

Table 1. Electrocardiographic Parameters

	Carriers	Non-Carriers
HR (beats/min)		
Age (yrs)		
0–1	144 ± 23 (7)	172 ± 25 (6)*
1–3	117 ± 28 (4)	127 ± 23 (10)
3–5	88 ± 9 (5)	102 ± 20 (12)
5–8	82 ± 13 (6)	90 ± 13 (13)
8–12	74 ± 19 (5)	82 ± 15 (18)
12–16	69 ± 14 (9)	79 ± 12 (13)
QRS width (ms)		
Age (yrs)		
0–1	49 ± 11	45 ± 8
1–3	73 ± 16	57 ± 13*
3–5	76 ± 11	55 ± 13*
5–8	82 ± 20	64 ± 11*
8–12	72 ± 11	66 ± 11
12–16	89 ± 19	73 ± 13*
% w/ST-segment elevation		
Age (yrs)		
0–1	14	0
1–3	0	10
3–5	40	42
5–8	83	38
8–12	100	44*
12–16	88	31*

Mean ± SD (n). *$p < 0.05$.
Carriers = with *SNC5A* gene mutation (1795insD); HR = heart rate; Non-Carriers = without *SNC5A* (1795insD).

Holter. Above one year, mean and lowest HR in the Holter were mostly lower in carriers (Table 2). Highest HR did not differ between the two groups (data not shown). Similarly >1 year QT at HR <110 to 120 beats/min were longer in carriers (Fig. 4). The QT after the longest pause and ΔQT were longer in carriers (Table 2); QT_c at the lowest HR for the whole group was longer in carriers than in non-carriers (0.47 ± 0.09 s vs. 0.36 ± 0.03 s; $p = 0.0000$). The differences in QT increase with age. Mean, lowest, and highest values of QT_c at the lowest HR and of ΔQT in both groups are shown in Figure 5. A QT_c of ≥0.44 at the lowest HR (sensitivity 100%; specificity 88.4%) and a ΔQT ≥60 ms (sensitivity 100%; specificity 82.6%) were good predictors for having LQT3. All carriers

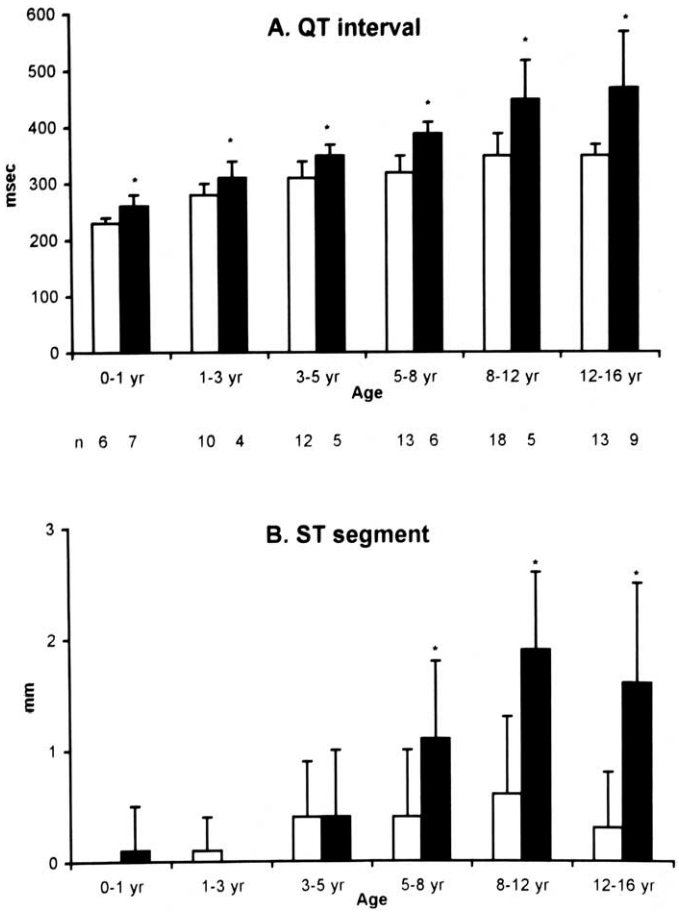

Figure 2. **(A)** QT interval for carriers **(solid bars)** and non-carriers **(open bars)** in different age groups. **(B)** ST-segment elevation. **Open bars** for 0 to 1 year and **solid bars** for 1 to 3 years are not visible, because the values are 0.0 ± 0.0 mm. Mean ± SD. *$p < 0.05$.

older than eight years of age had a ΔQT ≥60 ms. Wenckebach block was seen more often in carriers than in non-carriers (17.8% vs. 2.6%; $p < 0.05$), but the difference was not statistically significant in each age group owing to the small numbers (Table 2). No difference was found in rhythm disturbances.

Ergometry. There was no difference in highest HR (175 ± 9 beats/min vs. 179 ± 10 beats/min) and in QT at highest HR (0.23 ± 0.10 s vs. 0.22 ± 0.15 s) between carriers (n = 6) and non-carriers (n = 15). The QT at rest and during exercise at HR <110 beats/min was longer in carriers than in non-carriers. No ventricular arrhythmias occurred during or after exercise.

SAECG. The QRS width, D40, and V40 were higher, longer, and lower, respectively, in carriers (Table 3).

DISCUSSION

The onset of various electrocardiographic phenomena of a sodium channel defect (*SCN5A* mutation 1795insD) in a large family showed age-dependent penetrance: QT-prolongation and conduction defects are recognized from birth onward and become more pronounced during ageing, whereas right precordial ST-segment elevation becomes first apparent >5 years. It is known that both LQT3 and BS display age-dependent characteristics (8,9). In this family, QT prolongation is typically bradycardia-dependent and worsens with increasing age. This concurs with the youngest sudden death in this family at 14 years of age, a typical age for LQT3-related symptoms.

Right precordial ST-segment elevation, the hallmark of BS, was significantly more present in carriers >5 years and increased further until 12 years. To the best of our knowledge, there are no longitudinal studies on the electrocardiographic characteristics of BS. Yet, it is well known that the phenotype is most often recognized in male patients in their third to fourth decade (10,11). These data concur with a significantly lower electrographic penetrance in children compared with adults with an *SCN5A* mutation (17% vs. 100%) (16).

Right precordial ST-segment elevation is thought to result from transmural inhomogeneity in action potential (AP) configuration in the RV wall. Loss of the epicardial dome, among other potential consequences of a reduction in sodium-current amplitude, results in transmural current flow from endocardium to epicardium, picked up by the epicardial leads as ST-segment elevation. The mutation identified in this family significantly reduces sodium current by enhancing intermediate inactivation (17) and reduced membrane

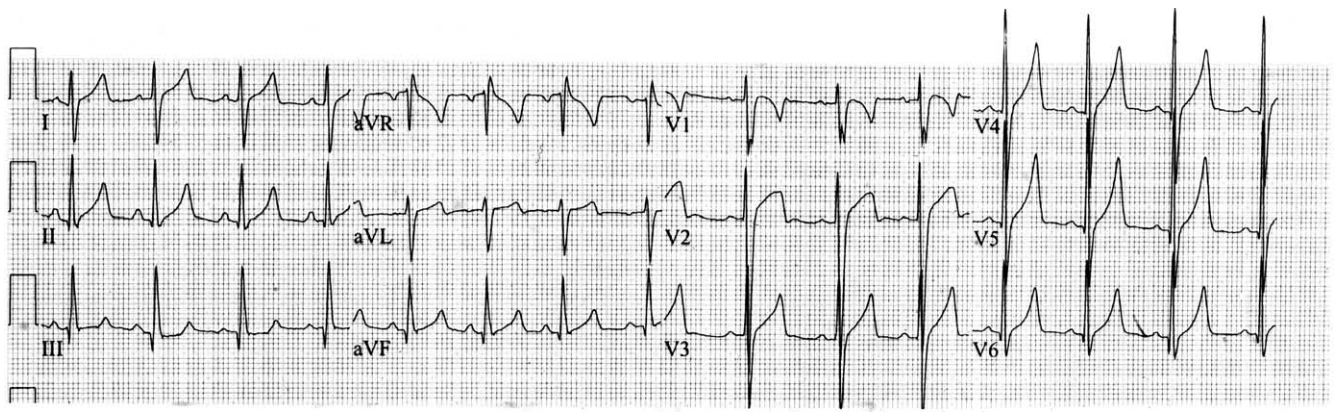

Figure 3. Electrocardiogram of a 12-year-old carrier showing ST-segment elevation in the right precordial leads.

Table 2. Holter Recording Parameters

	Carriers		Non-Carriers	
	Mean	**Lowest**	**Mean**	**Lowest**
HR (beats/min)				
Age (yrs)				
0–1	127 ± 14 (6)	72 ± 7	131 ± 22 (2)	80 ± 5
1–3	105 ± 12 (6)	60 ± 8	119 ± 12 (9)*	77 ± 12*
3–5	88 ± 4 (5)	51 ± 3	106 ± 22 (9)*	67 ± 16*
5–8	86 ± 6 (3)	50 ± 4	94 ± 7 (11)	63 ± 10*
8–12	75 ± 8 (8)	43 ± 5	84 ± 8 (19)*	52 ± 7*
12–16	70 ± 7 (8)	40 ± 4	82 ± 7 (17)*	49 ± 5*
QT (ms)	after pause	ΔQT	after pause	ΔQT
Age (yrs)				
0–1	350 ± 43	23 ± 15	300 ± 28	20 ± 8
1–3	430 ± 48	45 ± 38	329 ± 36*	9 ± 15*
3–5	508 ± 42	56 ± 17	350 ± 45*	13 ± 15*
5–8	567 ± 50	60 ± 40	376 ± 21*	10 ± 14*
8–12	630 ± 55	90 ± 25	397 ± 25*	14 ± 15*
12–16	670 ± 107	105 ± 53	400 ± 31*	13 ± 16*
Presence (%) of Wenckebach block				
Age (yrs)				
0–1	17		0	
1–3	0		0	
3–5	20		0	
5–8	33		0	
8–12	20		6	
12–16	25		0	

Mean ± SD (n). *$p < 0.05$.
QT = QT interval; other abbreviations as in Table 1.

expression of the mutant channel (unpublished data, C. Bezzina, July 2004). The contribution of the transient outward current (I_{to}) is crucial to this sequence of events, and developmental changes in I_{to} amplitude have been shown in canine epicardium (18). In dogs, I_{to} amplitude and density change with age, thereby significantly influencing the AP morphology of the epicardial AP in the first year of life. If similar changes occur in humans, it is well conceivable that the gradual increase in ST-segment amplitude is caused by a gradual age-dependent increase in epicardial I_{to} current. In the presence of reduced sodium current, an increase in I_{to} might eventually lead to loss of the epicardial plateau phase. Alternatively, an age-dependent reduction in sodium current might be present. The age-dependent increase in QRS width (Table 1) might reflect this. It has also been shown that, in adults, ageing impacts on conduction slowing in *SCN5A* mutant carriers (19).

The gradual increase in QT prolongation is less well explained. For this mutation, QT prolongation results from enhanced persistent sodium current (6). It is difficult, if not impossible, to predict the effect that age-dependent alteration in ion currents, including I_{to}, has on AP-duration. Hence, a good explanation is not readily available. Gender-specific differences were not observed; this may be explained by the small hormonal differences in prepubertal children.

Although none of the children with LQT3 in this family had any complaints, LQT3 can be a serious illness with sudden death as first manifestation (8). Whether ventricular arrhythmias or conduction disturbances are responsible for sudden death in this family is not known yet. In two symptomatic adults of this family, progressive cardiac conduction disturbance and prolonged asystole were found, which raises the possibility of a bradycardic mode of death (7). In the children, more Wenckebach block at night in the carriers was found. This is a very special phenomenon, because it is normally only seen at ages >9 years. Furthermore, it may be a serious triggering event for death, because of the provoking bradycardia and associated QT prolongation. Although the phenotype of the *SCN5A* mutation in the family evaluated is already present at very young age, the youngest child that died was 14 years old; however, other *SCN5A* mutations have been described as leading to sudden infant death syndrome (SIDS) or near-SIDS (20–23).

Before the mutation was detected in this family, we followed the children clinically and only treated them with pacemaker implantation when there were signs of extreme bradycardia or QT prolongation after pauses during the night. But because serious events in LQT3 can manifest in neonates, and because the results of our study demonstrate the occurrence of nocturnal bradycardias and QT prolongation even in the youngest children, the age at which the children should be treated with pacemaker implantation is questionable.

The adults in this family were prophylactically treated with an anti-bradycardia pacemaker as a preventive measure against sudden death. In adults, this strategy proved to be effective, because there were no more cases of sudden unexplained death in carriers who were treated with a

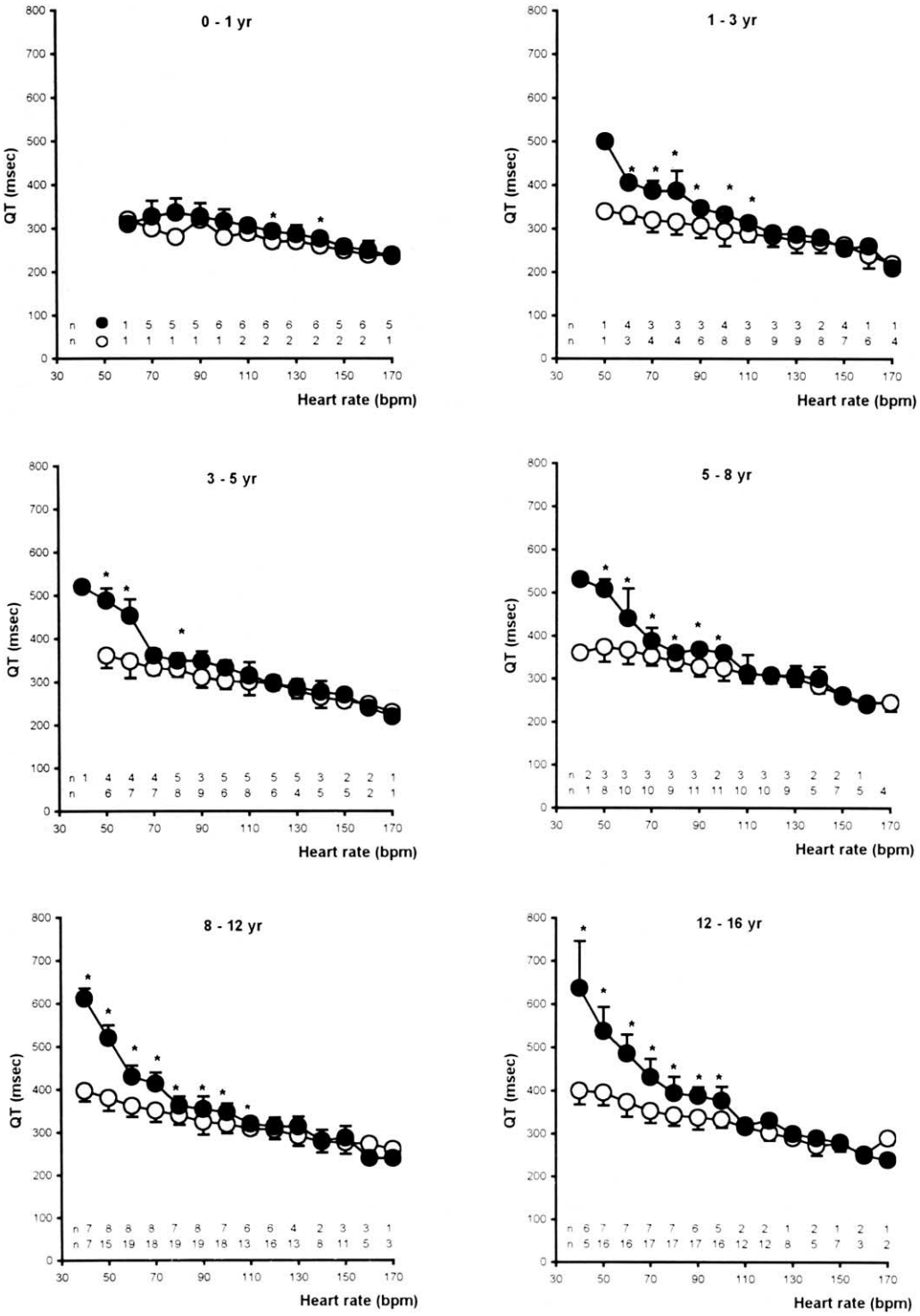

Figure 4. Relation between heart rate and QT interval for carriers **(solid circles)** and non-carriers **(open circles)** in different age groups. Mean ± SD. *$p < 0.05$. bpm = beats per minute.

pacemaker (n = 30), while five sudden deaths occurred among the remaining 30 carriers without a pacemaker (7). Therefore, it is our policy now to insert anti-bradycardia pacemakers in the children as well, partly because the first symptom is nocturnal death and partly because of the anxiety of the parents. None of the children with a pacemaker died. We therefore consider implantable cardioverter-defibrillator therapy, which could be considered even in small children (7,10,24), not necessary. Beta-blockers seem less effective in LQT3 patients (9), and with flecainide, clear augmentation of ST-segment elevation has been observed (25).

Our study demonstrates that LQT3 can be diagnosed with clinical tools at very young age in this family. The easiest way to confirm the diagnosis in this family is to

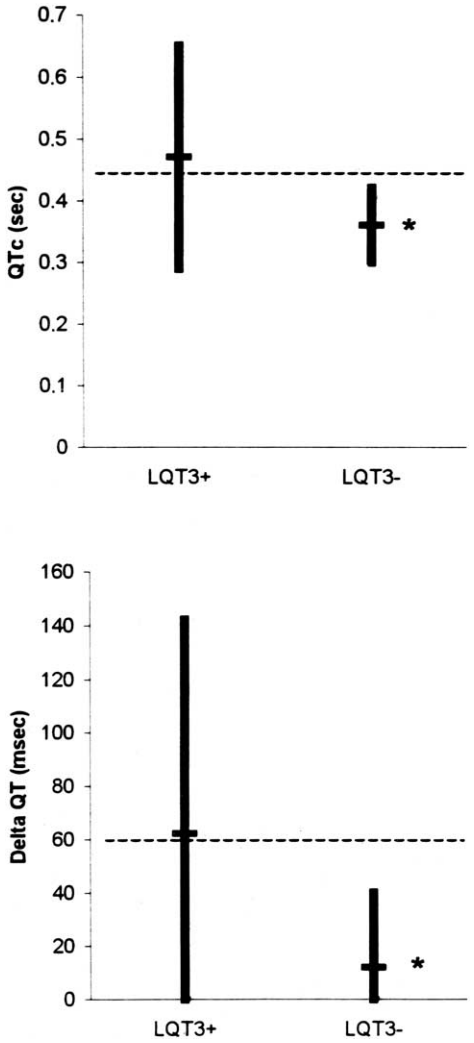

Figure 5. Mean, lowest, and highest values of QT_c interval at the lowest heart rate and of ΔQT interval in Holter recordings. The **dotted lines** represent the cut-off values for QT_c and ΔQT between long QT syndrome type 3 carriers (LQT3+) and non-carriers (LQT3−). *$p < 0.05$.

perform genetic analysis, because the mutation is known. But for other families in which a mutation has not been identified yet, it is useful to know which clinical tools contribute to the diagnosis of LQT3 at young age. Good clinical parameters for this diagnosis are the QT on an ECG, the QT, QT_c and ΔQT in a Holter, especially when focusing on the low HR at night and after pauses. Ergometry does not contribute to the diagnosis.

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Table 3. Signal-Averaged Electrocardiographic Parameters

	Carriers	Non-Carriers
QRS width (ms)		
Age (yrs)		
5–8	92 ± 9 (3)	88 ± 7 (5)
8–12	94 ± 11 (6)	84 ± 9 (15)*
12–16	106 ± 13 (3)	93 ± 9 (12)*
D40 (ms)		
Age (yrs)		
5–8	27 ± 12	18 ± 4
8–12	32 ± 11	19 ± 5*
12–16	38 ± 11	22 ± 7*
V40 (μV)		
Age (yrs)		
5–8	47 ± 45	70 ± 27
8–12	39 ± 21	117 ± 104*
12–16	22 ± 5	80 ± 56*
LP (%)		
Age (yrs)		
5–8	33	20
8–12	67	13*
12–16	100	25*

Mean ± SD (n). *$p < 0.05$.

D40 = time in which the voltage <40 μV at end of QRS interval; LP = late potentials; V40 = root mean square voltage for terminal 40 ms of QRS interval; other abbreviations as in Table 1.

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